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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/403,262	01/05/2000	NIKOLAUS THERES	11216/002001	7039

7590

09/12/2003

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EXAMINER

MEHTA, ASHWIN D

ART UNIT

PAPER NUMBER

1638

27

DATE MAILED: 09/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/403,262

Applicant(s)

THERES, NIKOLAUS

Examiner

Ashwin Mehta

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12 May 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 23 and 25-42 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 23 and 25-42 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 18 December 2002 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner. See PTO-948
mailed 1/23/03
Paper #18
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other:

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DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12 May 2003 has been entered.
2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
3. The rejections of claims 32 and 35-37, under 35 U.S.C. 112, regarding the term "modified" in claim 32 and the recitation "wherein the integrating step further comprises integrating" in claim 35, are withdrawn in light of the claim amendments.

Drawings

4. Applicants are reminded that drawing corrections, as required by the Draftsperson in the PTO-948 attached to the Advisory Action mailed on 18 June 2002, are due with the reply to the instant Office action. Failure to comply will result in ABANDONMENT of the application. See 37 CFR 1.85(a).

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Claim Objections

5. Claims 27-29, 31, 32, 40, and 41 remain objected to for the reasons of record stated in the Office action mailed 18 June 2002 under item 9.

Claim Rejections - 35 USC § 112

6. Claims 23 and 25-42 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the reasons for record stated in the Office action mailed 23 January 2003 and 18 June 2002. Applicant traverses the rejections in the paper filed 12 May 2002. Applicant's arguments have been fully considered but were not found persuasive.

It is first noted that Applicant indicated that claims 23-42 are pending, and that claim 24 is rejected under 35 U.S.C. 112, 2nd paragraph, for the term "stringent hybridization" (response, page 2, 2nd and 3rd full paragraphs). It is noted that Applicant cancelled claim 24 in the paper filed 18 December 2002. With the filing of the RCE, the paper filed 18 December 2002 was entered, and claim 24 was cancelled.

In the Office action mailed 18 June 2002, it was noted that claim 23 was indefinite for the recitation "high stringency." In the response submitted 12 May 2003, Applicant argues that page 29 of the specification indicates that reduced stringency includes 55°C, and that high stringency would thus be higher than this figure (page 2, 3rd full paragraph). However, the specification does not define that anything above 55°C is a high stringency condition. Further, a temperature of, for example, 56°C, is not considered in the art to contribute to high stringency conditions. Applicant also argues that one of skill in the art can select not only temperature, but also ionic

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strength and wash conditions, and still achieve "high stringency" (page 2, 3rd full paragraph).

However, one cannot know if they have selected a high stringency condition, if the specification does not define it.

Claim 23, and those dependent thereon, remain indefinite for the recitation, "derivative."

Applicant indicates that he believes that the only remaining rejection under 35 U.S.C. 112, 2nd paragraph, is the one discussed above (response, page 2 3rd full paragraph). However the rejection in the Office action mailed 18 June 2002 under item 10 remains.

Further in claim 23: it is not clear if the isolated nucleic acid comprises both the nucleic acid of (a) and the fragment or derivative of (b). If it comprises both, it is suggested that the conjunction, --and--, be inserted in line 5 after "formation;". If it comprises only one of the two, it is suggested that --or-- be inserted in line 5 after "formation;".

In claims 25 and 26: the claims are indefinite because, while they limit the polypeptide or nucleic acid mentioned in claim 23, they do not clearly indicate if the fragment or derivative of claim 23 is still encompassed.

In claims 35 and 36: the recitation "relative to an endogenous sequence" renders the claim indefinite. It is not clear orientation the nucleic acids are in, given that parent claim 23 encompasses nucleotide sequences encoding polypeptides, fragments and derivatives of thereof, and complements of the nucleotide sequences. It is also not exactly clear what endogenous sequences the recitations are referring to.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

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pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 23 and 25-42 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record stated in the Office action mailed 23 January 2003. Applicant traverses the rejection in the paper submitted 12 May 2003. Applicant's arguments have been fully considered but were not found persuasive.

Applicant argues that the claimed derivatives hybridize to SEQ ID NO: 1 under highly stringent conditions and that any deletion, substitution or addition is not encompassed. Applicants also argue that "highly stringent" is defined by the specification as higher than 50oC (response, page 3, 3rd full paragraph). However, as discussed above, "highly stringent" is not defined by the specification. Applicant also again argues that examples are not required, and that one of skill in the art would not doubt that derivatives satisfying the limitations of the claims could be created (response, page 3, 4th full paragraph). However, methods of making a product do not described the product itself. See Fiers vs. Sugarno, 25 USPQ 2d (CAFC 1993) at 1606, which states that "[a]n adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself'.

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8. Claims 23 and 25-42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Amended claim 23 indicates that the fragment or derivative of said nucleic acid or said complementary nucleic acid hybridizes with said nucleic acid or said complementary nucleic acid under "highly stringent conditions." There is no written description support for the recitation, "highly stringent conditions." This represents **NEW MATTER**, and must be removed from the claim.

9. Claims 23 and 25-42 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the reasons of record stated in the Office action mailed 23 January 2003. Applicant traverses the rejection in the paper submitted 12 May 2003. Applicant's arguments have been fully considered but were not found persuasive.

Applicant again argues that one of ordinary skill in the art would accept, on its face, that the Ls gene is involved in shoot, petal, and abscission zone formation, and that, as such, it would be acknowledged that increasing the expression of the Ls gene would lead to increased shoot, petal, and abscission zone formation. Applicant argues that evidence to support the conclusion

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that one of skill in the art could not predict the phenotype of transgenic plants expressing Ls genes has not been offered (response, page 4, 2nd paragraph). The specification teaches that cosmids containing the Ls gene complemented Ls mutant plants for the formation of side shoots, petals and abscission zone (page 16). This was acknowledged by the Examiner in the Office action mailed 13 September 2001, and that the Ls gene is involved in side shoot, petal, and abscission zone formation in non-transgenic plants is not the issue. However, those skilled in the art would not automatically assume that overexpression of a gene whose function is known would definitely enhance that function in a transgenic plant. The Office action mailed 13 September 2001 cited an example of a transgenic plant transformed with a gene that already had an endogenous copy of it, and wherein the transgenic plant did not display an enhanced function of that gene. The instant specification indicates that transgenic plants transformed with the Ls cDNA in sense orientation have been made (Example 7). However, the specification does not teach the phenotype of that transgenic plant. One cannot use the claimed method and the plants transformed with the claimed nucleic acid in sense orientation if the phenotype of that plant is not known.

Applicant also again argues, regarding the lack of enablement of fragments and derivatives, that one of skill in the art is more than capable of making small deletions, insertions, truncations, fusions, etc., each of which retain the ability to promote shoot, petal, and abscission zone formation (response, paragraph bridging pages 4-5). However, that the procedure for making a fragment or an insertion in a nucleotide sequence, is known in the art is not the issue. The specification does not provide any such guidance as to how the structure of SEQ ID NO: 2 may be changed without affecting its activity. The specification does not make any suggestions at

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all as to the sequences that are dispensable, sequences that may be substituted without affecting activity, what SEQ ID NO: 2 should be fused to, etc.

A declaration signed by the inventor, Dr. Nikolaus Theres, has been submitted which indicates that a nucleotide sequence encoding an "HA" tag was inserted at the 5' end of the Ls coding sequence, and that this sequence was used to transform a tomato lateral suppressor mutant. Of 14 transgenic lines produced, 9 lines showed some complementation of the mutant phenotype, whereas 5 showed a low degree of side-shoot and petal development (response, paragraph bridging pages 5-6 and declaration, items 4 and 5). However, this does not enable all derivatives encompassed by the claims.

The declaration also indicates that a homologous gene from Arabidopsis, termed "LAS," encodes a protein having 50.5% identity with the tomato gene and functionally complemented a tomato Ls mutant (response, page 6, 1st full paragraph and declaration, items 6 and 7). The declaration also indicates that a CaMV enhancer and Ls promoter were used to drive expression of the Ls gene product in a mutant Ls tomato plant. Partial complementation of the phenotype was obtained. Applicant's arguments indicate that these experiments address the issue of the enablement rejection drawn towards a lack of phenotype of transgenic plants (response, paragraph bridging pages 6-7 and declaration, items 8 and 9). As discussed above, that Ls genes can complement Ls mutant plants when transgenically expressed therein is not in dispute. However, the method claims are not limited to complementing Ls mutant plants, but encompass increasing or suppressing side-shoot, petal, and abscission zone formation in wild type plants as well. The declaration does not address the phenotype type of wild type plants transformed with the claimed nucleotide sequences.

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Regarding claim 37, the specification does not enable one skilled in the art to cause the integration of any nucleic acid molecule into a genomic region of a homologous endogenous gene by homologous recombination. The specification, on page 20, lines 8-10, cites Miao and Lam et al. (Plant J., 1995, Vol. 7, pages 359-365) for teaching a method for homologous recombination in plants. However, Miao et al. reported only a single targeting event, in only one plant, Arabidopsis. The instantly claimed method is not limited to use in only Arabidopsis plants. This single report is not an indication that this method is routine. Miao et al. themselves stress that homologous recombination "may become routine in the near future" (page 363), which indicates that their method cannot routinely be used in all plant types, with all nucleic acid sequences. Puchta (Plant Mol. Biol., 2002, Vol. 48, pages 173-182) discusses the state of gene replacement by homologous recombination in plants, and teaches that efficient gene targeting techniques in higher plants have not yet been achieved. Puchta teaches, for example, that improvements to gene targeting in animals have not been successful in plants (page 173), that extending the length of homology in the transferred DNA to up to 22 kb did not result in higher frequencies (page 174). Puchta also discusses the experiments of Miao et al. in which one callus out of 2580 tissue culture transformants was isolated, in which targeting of the *TGA2* locus had occurred, and that the callus was a chimera and could not be regenerated (page 174). Puchta also discusses that another report of gene targeting in Arabidopsis, involving the *AGL5* MADS-box gene, has been controversial and that no statistically sound conclusion as to the frequencies of targeting could be drawn from this event (paragraph bridging pages 174-175). Terada et al. (Nature Biotech., 2002, Vol. 20, pages 1030-1034) also address reports of gene targeting in Arabidopsis, and also assert that no one has yet repeated the experiments, and that the authors of

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one of those reports also detected the occurrence of undesirable events, including ectopic recombination and/or simultaneous ectopic integration of the transgene used (page 1030). While Terada et al. present a method for homologous recombination in rice, it is noted that this method was not known at the time the instant invention was filed. As homologous recombination is required to practice the claimed method in all plant species, and that repeatable methods of gene targeting through homologous recombination in plants were not known in the art at the time of the instant invention, undue experimentation would be required by one skilled in the art to use the claimed method to integrate the claimed nucleic acid molecule into the region of a homologous endogenous gene by homologous recombination in any and all plants species. Further, the specification as filed does not teach the sequences of homologous endogenous Ls genes for plant species other than tomato. See Genentech, Inc. V. Novo Nordisk, A/S, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997), which teaches that “the specification, not the knowledge of one skilled in the art” must supply the enabling aspects of the invention.

10. Claims 23 and 25-42 remain rejected.

Contact Information

Any inquiry concerning this or earlier communications from the examiner should be directed to Ashwin Mehta, whose telephone number is 703-306-4540. The examiner can normally be reached on Mondays-Thursdays and alternate Fridays from 8:00 A.M to 5:30 P.M. If attempts to reach the examiner by telephone are unsuccessful, the examiner’s supervisor, Amy Nelson, can be reached at 703-306-3218. The fax phone numbers for the organization where this

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application or proceeding is assigned are 703-305-3014 and 703-872-9306 for regular communications and 703-872-9307 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

September 3, 2003

A handwritten signature in black ink, appearing to read 'Ashwin D. Mehta', written in a cursive style.

Ashwin D. Mehta, Ph.D.
Primary Examiner
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